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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/756,125	01/12/2004	Dennis R. Burton	48503-00004	3579

23767 7590 01/30/2007
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EXAMINER	
CHEN, STACY BROWN	
ART UNIT	**PAPER NUMBER**
1648	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/30/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/756,125	BURTON ET AL.	
	Examiner	Art Unit	
	Stacy B. Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *11-14,30-33,49-52 and 68-71* is/are withdrawn from consideration.

5)☒ Claim(s) *1,2 and 15* is/are ~~allowed~~. allowable. SBC 1/25/07

6)☒ Claim(s) *16,17,19,21,29,35,36,38-41,47,53-55,57-60,66,72-74,76,85 and 95* is/are rejected.

7)☒ Claim(s) *9,20,22,28 and 34* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's after-final amendment filed December 12, 2006 is acknowledged and entered. The notice of appeal filed December 12, 2006 is acknowledged. Upon further consideration of the claimed subject matter, the finality of the Office action of June 13, 2006 is withdrawn. The rejections of claims 10, 48, 67, 77-79, 86 and 91-93 under 35 U.S.C. 112, first paragraph, are moot in view of the cancellation of these claims. This Office action presents new grounds of rejection and is non-final. Any inconvenience is regretted.

2. Claims 1-3, 9, 11-17, 19-22, 28-36, 38-41, 47, 49-55, 57-60, 66, 68-74, 76, 85 and 95 are pending. Claims 11-14, 30-33, 49-52 and 68-71 are withdrawn from consideration, being drawn to non-elected subject matter. Claims 1-3, 9, 15-17, 19-22, 28, 29, 34-36, 38-41, 47, 53-55, 57-60, 66, 72-74, 76, 85 and 95 are under examination.

Claim Objections

3. Claims 9, 20-22, 28, 34, 35, 38, 39, 54, 55 and 72-74 are objected to for minor informalities:

- Claims 54, 55 and 72-74 are objected to for reciting non-elected subject matter relating to nucleic acid embodiments.
- Claims 20-22, 28, 34 and 35 recite awkward language, "all of the light chain CDR amino acids sequences of SEQ ID NO: 4". Suggested language is "all of the light chain CDR sequences of SEQ ID NO: 4".

- Claim 38 recites awkward language, "all of the light chain CDR amino acid sequence of SEQ ID NO: 4". Suggested language is "all of the light chain CDR sequences of SEQ ID NO: 4".
- Claim 9 refers to an antibody having at least one variable region comprising an amino acid sequence set forth in SEQ ID NO: 4. In order to avoid interpretation of "at least one variable region comprising an amino acid sequence" [emphasis added] to read on fragments of SEQ ID NO: 4, it is suggested that the claim be amended to recite, "at least one variable region comprising the amino acid sequence set forth in SEQ ID NO: 4" [emphasis added].

Claim Rejections - 35 USC § 101

4. (*New Rejection*) Claims 19, 38, 57, 76 and 95 refer to the use of transgenic animals, which encompasses the use of transgenic humans. Transgenic humans, making transgenic humans and uses of transgenic humans are non-statutory subject matter. Suggested language to overcome this amendment, provided there is support in the specification as originally filed, is "non-human transgenic animal".

Claim Rejections - 35 USC § 112

5. (*New Rejection*) Claims 39, 41, 47, 53-55, 57-60, 66, 72-74 and 76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 47 recites, "A composition comprising at least one isolated mammalian anti-Dengue virus antibody having at least one light chain CDR having the amino acid sequence of at least one of SEQ ID NO: 4". Since SEQ ID NO: 4 is the only amino acid sequence recited in the claim, "at least one of SEQ ID NO: 4" is not appropriate language. Further, it is unclear how the antibody in the composition has at least one light chain CDR having SEQ ID NO: 4, since SEQ ID NO: 4 contains three variable light chain CDRs. The claim reads on a single CDR that contains the sequence of three CDRs. It appears that Applicant may intend for the antibody to have at least one of the three CDRs in SEQ ID NO: 4. Correction/Clarification is required. Claims 39, 41, 53-55, 57-60, 66, 72-74 and 76 recite similar language that must be corrected.

6. (*New Rejection*) Claims 3, 21, 40, 59 and 60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody comprising a variable light chain comprising SEQ ID NO: 4 that binds Dengue NS-1, does not reasonably provide enablement for an antibody comprising a variable light chain comprising SEQ ID NO: 4 that binds any non-NS1 Dengue NS protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims encompass an antibody comprising SEQ ID NO: 4 that binds to any Dengue non-structural protein, of which there are seven (Seema and S. K. Jain, *Indian Journal of Clinical Biochemistry*, 2005, 20(2):92-103, see page 96, second column, first full paragraph). The specification does not disclose that the antibody comprising SEQ ID NO: 4 is capable of binding to any NS protein, but specifically to NS-1. Similarly, with respect to claim 60,

Extending the function of the claimed antibody from binding to NS-1 to substantially neutralizing an activity of any Dengue virus protein is not supported by the specification. The only protein that will be bound by the antibody is NS-1. The effect of this binding activity on the remaining Dengue proteins is not known. Therefore, according to the specification, an antibody comprising a light chain having the amino acid sequence of SEQ ID NO: 4 will bind to Dengue NS-1 protein (page 3, lines 23-24). The disclosure is not commensurate in scope with the breadth of the claims.

7. (*New Rejection*) Claims 16, 17, 29, 35, 36, 54, 55, 73 and 74 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antibodies for diagnostic uses in humans, does not reasonably provide enablement for antibodies that impart a therapeutic benefit to a human (pharmaceutical uses in humans). The specification also fails to enable a composition comprising a prophylactically effective amount of at least one compound or protein listed in claim 29. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims encompass antibodies and compositions/devices comprising the antibodies that bind Dengue NS-1 protein. The term "pharmaceutical" implies that the claimed compositions must impart some therapeutic benefit to the recipient. The nature of the pharmaceutical aspect of the invention is the use of anti-NS-1 antibodies to bind Dengue virus to reduce infection and disease in an individual. While the claimed antibodies are capable of binding NS-1, there is no evidence in the specification that the antibodies are capable of reducing infection or treating an

existing infection. Experiments in appropriate animal models using the passive therapy would be evidence that the claimed antibodies are capable of imparting therapeutic benefit to patients.

Peng *et al.* (*Dengue Bulletin*, 2004, 28:168-173) reviews the animal models available for use in studying Dengue infections. In addition to disclosing that the mechanisms involved in the pathogenesis of Dengue virus infection/disease is poorly understood, Peng also discloses that no effective vaccine is available to prevent the infection (abstract). Peng teaches that while there are some small animal models for Dengue virus infection, none of them mimic the manifestations seen in humans (page 171, second column, last paragraph). Peng discloses that more information at the molecular level is required before an animal model can be developed for use in vaccine development. Shresta *et al.* (*J. Virology*, 2006, 80(20):10208-10217) disclose a murine model for Dengue virus-induced lethal disease with increased vascular permeability. Shresta *et al.* teaches that the lack of an appropriate animal model for dengue virus has impeded studies in disease pathogenesis (abstract). Shresta *et al.* discloses the development of a murine model that exhibits increased vascular permeability, an important advance in developing animal models that more closely mimic human disease.

Given the breadth of the claims, the nature of the invention, the state of the art, the high level of skill in the art, the low level of predictability (lack of an animal model), lack of working examples and limited guidance provided in the specification, it would require undue experimentation to use the claimed antibodies as pharmaceuticals.

8. (*New Rejection*) Claim 29 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claim is drawn to a composition comprising antibodies to Dengue NS1, and a therapeutically or prophylactically effective amount of at least one compound or protein selected from the group consisting of a detectable label or reporter, a Dengue virus replication antagonist, a non-steroid anti-inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anesthetic, and antimicrobial, a corticosteroid, an erythropoietin, an antigen for immunization, an immunoglobulin, a growth hormone, a hormone replacement drug, a radiopharmaceutical, an asthma medication, an inhaled steroid, an epinephrine or analog, a cytokine, and a cytokine antagonist. *The claims encompass a large genus of molecules that are therapeutic or prophylactic, for which Applicant has not adequately demonstrated possession.*

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

In this case, the claimed composition comprises an anti-Dengue NS1 antibody and a molecule that imparts a therapeutic benefit, or a preventative benefit (prophylactic). While the claims do not mention exactly what is to be treated or prevented, the composition as a whole encompasses molecules that are not known to be therapeutic or prophylactic against Dengue virus, or any other pathogen.

For example, a therapeutic or prophylactic composition comprising anti-Dengue NS1 antibody in addition to an amount of any cytokine: What condition is the cytokine going to prevent? And, given the condition, what type of structural features and functions should the particular cytokine possess? In the case of a detectable label or reporter: What condition is that molecule going to treat or prevent, and what properties should the label have? These same questions apply to all of the molecules listed in the claims. Without a structure/function nexus, one of skill in the art would not be put in possession of the large genus of molecules encompassed by the claims.

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Claim Rejections - 35 USC § 102

9. (*New Rejection*) Claims 58-60 and 66 are rejected under 35 U.S.C. 102(b) as being anticipated by Valdés *et al.* (*Clinical and Diagnostic Laboratory Immunology*, 2000, 7(5):856-857, "Valdés"). The claims are drawn to isolated mammalian anti-Dengue virus antibodies and a composition thereof. The antibodies bind to the same region of a Dengue virus protein as an antibody comprising at least one light chain CDR of SEQ ID NO: 4. (Note that the structural components of the claims are addressed, not the non-enabled embodiments referred to in the rejection above). An antibody comprising SEQ ID NO: 4 binds NS-1.

Valdés discloses human Dengue antibodies against structural and nonstructural proteins, including antibodies against NS1 (abstract). The antibodies were isolated from patients infected

with Dengue virus. These antibodies are human and are therefore mammalian. With regard to the limitation that the composition comprises at least a pharmaceutically acceptable carrier or diluent (claim 85), the serum samples taken from the patients are comprised of serum (a pharmaceutical carrier) and anti-NS-1 antibodies.

10. (*New Rejection*) Claims 58-60, 66, 72-74, 76, 85 and 95 are rejected under 35 U.S.C. 102(b) as being anticipated by Flamand *et al.* (WO 00/75665 A1, the English translation will be referenced, U.S. Patent 6,870,032 B1, "Flamand"). The claims are drawn to isolated mammalian anti-Dengue virus antibodies and a composition thereof. The antibodies bind to the same region of a Dengue virus protein as an antibody comprising at least one light chain CDR of SEQ ID NO: 4. (Note that the structural components of the claims are addressed, not the non-enabled embodiments referred to in the rejection above). An antibody comprising SEQ ID NO: 4 binds NS-1. Also claimed are articles of manufacture and devices comprising the antibodies. Also claimed are isolated populations of monoclonal mammalian antibodies produced by a method comprising providing a host that expresses, in recoverable amounts, said antibodies.

Flamand discloses assays for diagnosing Flavivirus infection using antibodies with high affinity for NS1 protein in its hexameric form (soluble form). Flamand's monoclonal antibodies (populations) bind Dengue NS1 (col. 4, lines 24-62). The antibodies are disclosed as suitable for use as immunogenic compositions, further comprising pharmaceutically acceptable vehicles (col. 7, lines 17-25 and 48-53). Since Flamand discloses that the antibodies can be used for passive immunization, one would expect that the route of administration would be oral, intravenous, or any other suitable route. With regard to the limitation that the container be suitable for various

routes of delivery, the containers in which the antibodies are held, presumably vials, are suitable for delivery via the following routes: bolus, vaginal, rectal, buccal and sublingual. The antibodies are packaged in a kit or boxed set for diagnostic purposes, which necessarily contains containers comprising the antibodies (articles of manufacture), packaging materials, and pharmaceutically acceptable vehicles.

With regard to the method by which the monoclonal mammalian antibodies are produced (host cells, etc.), the method of production of the antibodies is not given patentable weight since the claims are drawn to products. Since Flamand's antibodies bind Dengue NS-1, the limitations of the claims have been met. Therefore, the claimed subject matter is taught by Flamand.

Conclusion

11. Claims 1, 2 and 15 are allowable. SEQ ID NO: 4 is free of the prior art of record.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Stacy B. Chen 1/25/07

STACY B. CHEN
PRIMARY EXAMINER

Continuation of Disposition of Claims: Claims pending in the application are 1-3,9,11-17,19-22,28-36,38-41,47,49-55,57-60,66,68-74,76,85 and 95.